REMARKS

Claims 1-8, 11-17, and 20-27 are pending in this application. Claims 3, 5-8, 14, 16-17, 22-25 and 27 have been amended. No new matter is introduced by these amendments, and no new issues are raised. Entry of the amendments after final action is appropriate because the amendments are believed to place the claims in a condition for allowance. Moreover, entry of the amendment would render the §112, ¶2 rejections moot and simplify issues for appeal.

Reconsideration of the pending prior art rejections is requested because the prior art would discourage the substitution of the claimed synthetic analogs for naturally occurring cardiolipin and lecithin. Moreover, data in the specification demonstrate that the claimed combination of tetramyristoyl cardiolipin and 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine provides unexpectedly superior results that would rebut any *prima facie* case of obviousness. In particular, an antigen including the claimed synthetic analogs provides superior sensitivity and selectivity in serological tests in comparison to an antigen containing naturally occurring cardiolipin and lecithin. This result is surprising and unexpected, at least, because the prior art taught that synthetic analogs were often ineffective substitutes for naturally occurring cardiolipin and lecithin in the antigen used in such serological tests.

Upon entry of this amendment, **claims 1-8, 11-17, and 20-27 will be pending in this application**. Consideration of the pending claims is requested.

Telephone Interview:

Applicants thank Examiner Shahnan Shah and Examiner Swartz for the courtesy of a telephone interview with their representative, Debra A. Gordon, on February 10, 2004. During the telephone conference, the obviousness rejections under 35 U.S.C. 103(a) were discussed. Applicants' representative requested clarification regarding the Office's basis for motivation to combine the references cited in the obviousness rejections. Examiner Shahnan Shah confirmed that the basis for each of the obviousness rejections was that tetramyristoyl cardiolipin and 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine are commercially available. Discussion ensued regarding whether commercial availability alone was sufficient basis to support a *prima*

facie case of obviousness. Secondary considerations relevant to the obviousness rejections were also discussed.

Agreement was not reached on the issues. Examiner Shahnan Shah invited Applicants to submit for her consideration a response presenting arguments, including those discussed during the interview.

Claim Rejections under 35 U.S.C. §112, 2nd paragraph:

Claims 3, 5-8, 14, 16-17, 22-25 and 27 have been rejected under 35 U.S.C. §112, 2nd paragraph in two separate rejections (see, paragraphs 14 and 18 of the Office Action) because the term "about" is allegedly indefinite. Applicants traverse these rejections for the reasons set forth in the Amendment and Response to Non-Final Office Action, mailed August 28, 2003 (the "August 28, 2003 Response"). However only to facilitate prosecution of the application, claims 3, 5-8, 14, 16-17, 22-25 and 27 have been amended to remove the term "about." Thus, these §112, ¶2 rejections are moot and should be withdrawn.

Claim Rejections under 35 U.S.C. §103:

Claims 1-8, 12-17, and 20-27 have been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Yabusaki, U.S. Pat. No. 4,738,932 ("Yabusaki") in view of Avanti Polar Lipids product no. 710332 ("Avanti 710332") and further in view of Avanti Polar Lipids product no. 850457 ("Avanti 850457"). Four separate §103(a) rejections were issued (see, paragraphs 15, 16, 19, and 20 of the Office Action); however, each rejection cites the same above-mentioned combination of references and each rejection is supported by the same justification. Thus, Applicants provide a collective response to all of the obviousness rejections. Applicants traverse each of the obviousness rejection for the reasons set forth in the August 28, 2003 Response and for the further reasons discussed below.

Applicants respectfully submit that the Patent Office has not established a *prima facie* case of obviousness. Arguments in support of this position are discussed in detail below. However, even if a *prima facie* case of obviousness had been established, the specification teaches that the claimed compositions and methods are unexpectedly superior to the antigen composition containing naturally occurring cardiolipin and lecithin (referred to as the "naturally

occurring antigen"), which is described, for example, in Yabasuki. Such unexpectedly superior results rebut any alleged *prima facie* case of obviousness.

The data in the specification demonstrate that an antigen composition comprising tetramyristoyl cardiolipin and 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine is unexpectedly superior to the naturally occurring antigen, which is described in the reference cited by the Office action. For example, when tested against serum reactive by the RPR Test (a standard, non-treponemal test for syphilis), the claimed synthetic antigen reacted with 100% of samples, while the naturally occurring antigen reacted with 88% of samples (see, for example, page 22, lines 1-4 of the specification). In quantitative testing, the claimed synthetic antigen had endpoint titres of 1/2 or 1 dilution better than the naturally occurring antigen in 85% of serums tested (see, for example, page 23, lines 12-14 of the specification). In blind testing of 495 serum specimens, the synthetic antigen was reactive with the same 38 samples that tested positive in direct tests for the syphilis-causing bacteria, *Treponema pallidum*. In comparison, the naturally occurring antigen identified only 36 of the 38 treponeme-positive cases (see, for instance, Example 7 of the specification). The superior sensitivity of the claimed composition is unexpected because, as discussed in detail below, the prior art teaches that antigens including synthetic analogs of cardiolipin or lecithin are generally less sensitive.

The factual evidence cited above, which is already of record demonstrates that the claimed composition (and, therefore, methods of use thereof) has unexpectedly superior selectivity and sensitivity. In particular, the claimed synthetic antigens surprisingly provide a more sensitive assay than an assay using the naturally occurring antigen. In addition, the amount of synthetic antigen necessary to obtain a positive response was less than the naturally occurring antigen in 85% of serums tested. Especially in light of the known failures of prior synthetic antigens, these unexpectedly superior results establish the non-obviousness of the claimed invention.

Even if the specification did not clearly establish the unexpectedly superior properties of the claimed antigen composition (and methods of use thereof), the Patent Office has not established a *prima facie* case of obviousness. As set forth in MPEP §2142, the burden is on the Patent Office (MPEP §2142) to establish a *prima facie* case of obviousness. To do this, the

Office must (among other things) present factual support for (i) a suggestion or motivation to combine the cited references' teachings; and (ii) a reasonable expectation of success. The teaching or suggestion to combine the cited references and the reasonable expectation of success must both be found in the prior art and cannot be based on Applicants' disclosure. If the Office cannot meet its burden and produce a *prima facie* case of obviousness, then an obviousness rejection should not be issued and/or an issued obviousness rejection cannot stand.

In the present case, the Office has neither proved a suggestion or motivation to combine the teachings of the cited references nor a reasonable expectation of success. The only rationale the Office offers for either of these elements of its *prima facie* case is that the individual components of the admittedly novel combination of tetramyristoyl cardiolipin and 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine are "known in the art and are commercially available" (see, Office Action at page 5, line 7; page 5, line 19; page 7, line 2; page 7, lines 13-14; page 8, line 19; and page 9, line 20).

Having found individual components of the combination claims to be commercially available, the Office action improperly places the burden on the Applicants to "provide[] a persuasive reason why one of ordinary skill in the art at the time the invention was made ***would not use*** the commercially available pure synthetic cardiolipin and lecithin powders . . . " (emphasis added; see, page 5, line 19 through page 6, line 2; and page 7, lines 14-18). In fact, the burden is on the Office to provide evidence why one of ordinary skill in the art at the time the invention was made ***would use*** the commercially available components in the claimed combinations. The Office has improperly shifted the burden of proof of an element of the Office's *prima facie* case to the Applicant. In doing so, the Office fails to prove a motivation to combine the cited references. Therefore, a *prima facie* case of obviousness has not been established, and the §103(a) rejections should be withdrawn on this basis alone.

It is possible that the Office action intended to allege that tetramyristoyl cardiolipin and 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine are known equivalents of naturally occurring cardiolipin and naturally occurring lecithin, respectively (see, MPEP §2144.06). Even if this is the position of the Office, the "equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or

mechanical equivalents" (MPEP §2144.06). The Office did not offer any proof of equivalency and, as discussed in the following paragraph, the prior art does not recognize any such equivalency.

As discussed during the February 10, 2004, telephone interview and as raised in the August 28, 2003 Response, it was known in the art at the time of the invention that replacing either naturally occurring cardiolipin *or* naturally occurring lecithin in the naturally occurring antigen (as described in Yabusaki) with a synthetic analog led to unpredictable results and often led to decreased activity of the antigen. At least two references that are already in the record make this point. For example, Barner (U.S. Pat. No. 4,307,074) states that "[cardiolipin] analogues as have been synthesized have demonstrated little or no activity in the serological syphilis test in comparison with [naturally occurring] cardiolipin . . . " (at column 1, lines 34-37). Similarly, Inoue and Nojima (*Chem. Phys. Lipids*, 3:70-77, 1960; reference D4 of the International Search Report), which describes a series of synthetic cardiolipins (*not including tetramyristoyl cardiolipin*; see, for example, Fig. 1), demonstrates that serum reactivity to antigens comprising different synthetic cardiolipins is quite unpredictable (see, for example, section entitled "Reactivity of antiserum against cardiolipin antigen" at pages 72-73). Thus, references already in the record establish that various synthetic cardiolipins could not predictably be substituted for naturally occurring cardiolipin in the naturally occurring antigen. Similarly, it was known in the art that antigens prepared with synthetic lecithins "were significantly less sensitive than those prepared with an equimolar amount of natural lecithin" (Reyn and Bentzon, *WHO Bull.*, 14:567-576, 1956; citation taken from the Synopsis on page 567; attached as Exhibit A). The foregoing references (as well as others not entered) make clear that synthetic analogs could not be predictably substituted for naturally occurring cardiolipin or naturally occurring lecithin in the naturally occurring antigen without a substantial loss in sensitivity. Hence, synthetic analogues of cardiolipin or lecithin were not equivalents of the respective naturally occurring compounds.

In summary, the Office has not offered any proof of the equivalence of tetramyristoyl cardiolipin and 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine with naturally occurring cardiolipin and naturally occurring lecithin, respectively, nor does the prior art support any

equivalence of such compounds. As a result, equivalency cannot serve as the basis for the present obviousness rejections.

Even though the foregoing arguments alone (or together) should suffice to overcome the obviousness rejections, the cited references are also improperly combined because the prior art teaches away from the combination (see, MPEP §2145(X)(D)(2)). As discussed above, it was known that (i) synthetic analogs were poor (if any) substitutes for naturally occurring cardiolipin or naturally occurring lecithin, and (ii) even one synthetic analog could reduce the activity of the desired antigen composition. Such uncertainty teaches away from antigen compositions having even *one* synthetic analog. Such teaching away would be that much greater for an antigen composition comprising *two* synthetic analogs, such as the claimed combination of tetramyristoyl cardiolipin and 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine. Despite the contrary teachings in the art, the Applicants forged ahead and were ultimately successful, which also is "evidence of nonobviousness" (MPEP §2145(X)(D)(3)). Because the prior art teaches away from the claimed combination of tetramyristoyl cardiolipin and 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine, the references are not properly combined; thus, the Office does not satisfy all the elements of it *prima facie* case of obviousness and the §103(a) rejections should be withdrawn on, at least, this ground.

For the same reasons that the prior art teaches away from or discourages the claimed compositions and methods, there was no reasonable expectation that a combination of the cited references would lead to a successful antigen composition. As discussed above, the prior art was replete with unsuccessful antigens having only *one* synthetic analog of cardiolipin or lecithin; thus, even if one of ordinary skill in the art came upon the cited combination of references, s/he had no reasonable expectation that an antigen composition including *two* synthetic components (and methods of use thereof) would be successful. Without a factual basis for a reasonable expectation of success, a *prima facie* case of obviousness cannot be (and has not been) established. Thus, the §103(a) rejections should be withdrawn on, at least, this ground.

At best, the Office Action improperly suggests it would have been "obvious to try" to make the claimed compositions and methods. As explained in MPEP §2145(X)(B), "obvious to try" is no rationale for combining Yabusaki, Avanti 710332, and Avanti 850457. Yabusaki

describes an antigen comprising naturally occurring cardiolipin and naturally occurring lecithin. As discussed during the February 10, 2004, telephone interview and as raised in the August 28, 2003 Response, there are hundreds (or perhaps more) possible synthetic variations of both cardiolipin and lecithin. Taken together, there may be thousands of possible combinations of synthetic analogs of cardiolipin and lecithin. The prior art provided no direction as to which of the many possible choices was likely to be successful at least because (as discussed above) antigen compositions with synthetic cardiolipin or lecithin analogs did not have the specificity and/or sensitivity of the antigen with naturally occurring components. Because obvious-to-try is not a permissible basis for combining references, the §103(a) rejections should be withdrawn on, at least, this ground.

In summary, the Office has improperly shifted the burden of proving a motivation to combine the cited references, has not provided a motivation to combine the cited references (or has provided an improper motivation, such as obvious to try), and has failed to support a reasonable expectation of success even if the cited references were combined. For all of the foregoing reasons, the Office has not met its burden for establishing a *prima facie* case of obviousness, and the §103(a) rejections should be withdrawn. In addition, the specification demonstrates the unexpectedly superior sensitivity of the claimed combination of tetramyristoyl cardiolipin and 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine when compared to the naturally occurring antigen set forth in the Yabusaki reference. Thus, even if a *prima facie* case of obviousness was made, it has been rebutted, and the §103(a) rejections should be withdrawn.

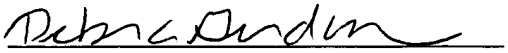
In light of all of the foregoing arguments, Applicants respectfully request that each of the §103(a) rejections be reconsidered and withdrawn.

CONCLUSION

It is respectfully submitted that the present claims are in a condition for allowance. If it may further issuance of these claims, the Examiner is invited to call the undersigned at the telephone number listed below.

Respectfully submitted,

KLARQUIST SPARKMAN, LLP

By 

Debra A. Gordon, Ph.D., J.D.
Registration No. 54,128

One World Trade Center, Suite 1600
121 S.W. Salmon Street
Portland, Oregon 97204
Telephone: (503) 226-7391
Facsimile: (503) 228-9446